Pulmonary Renal Syndromes

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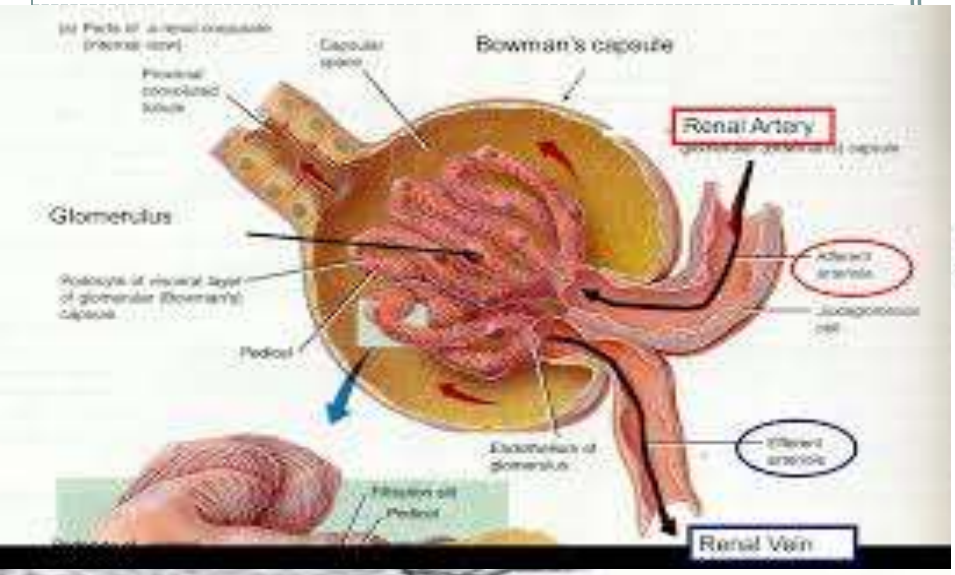
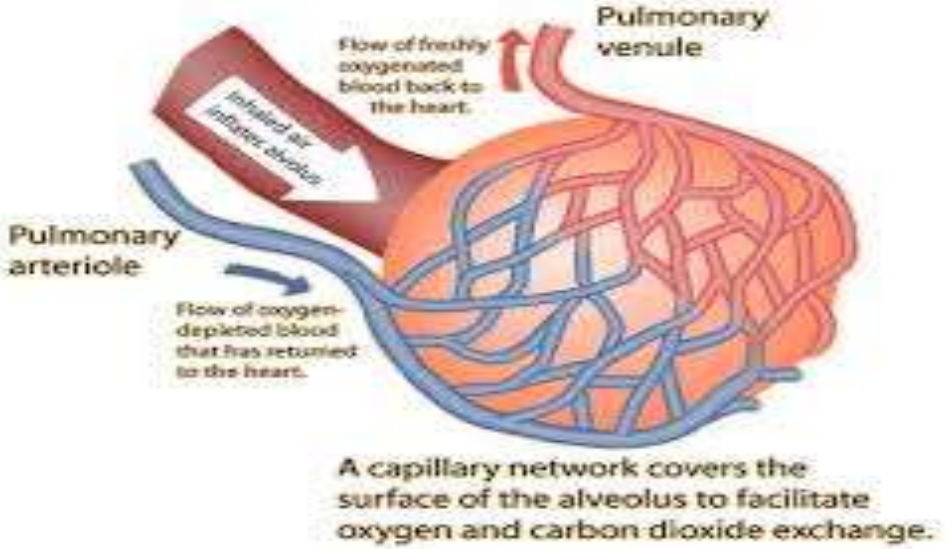
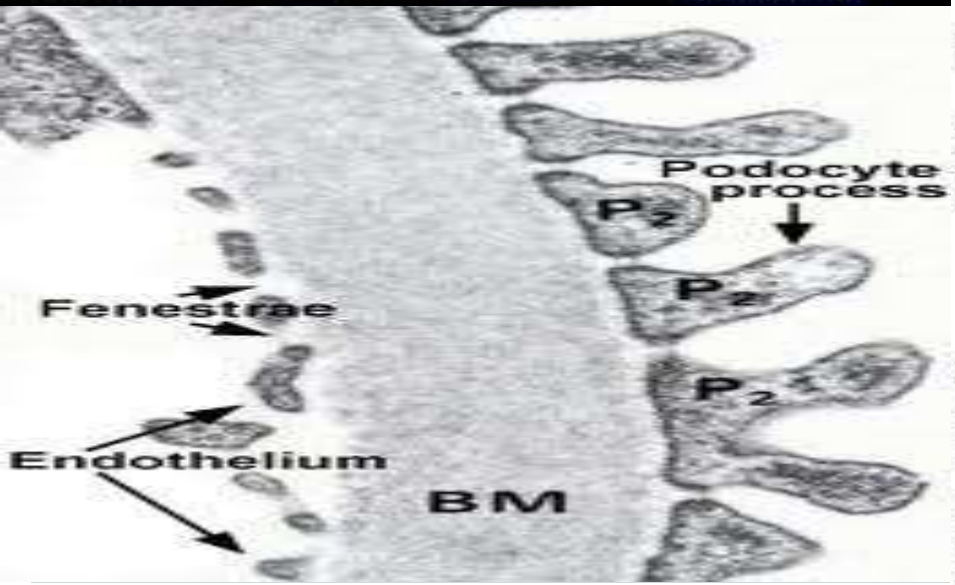
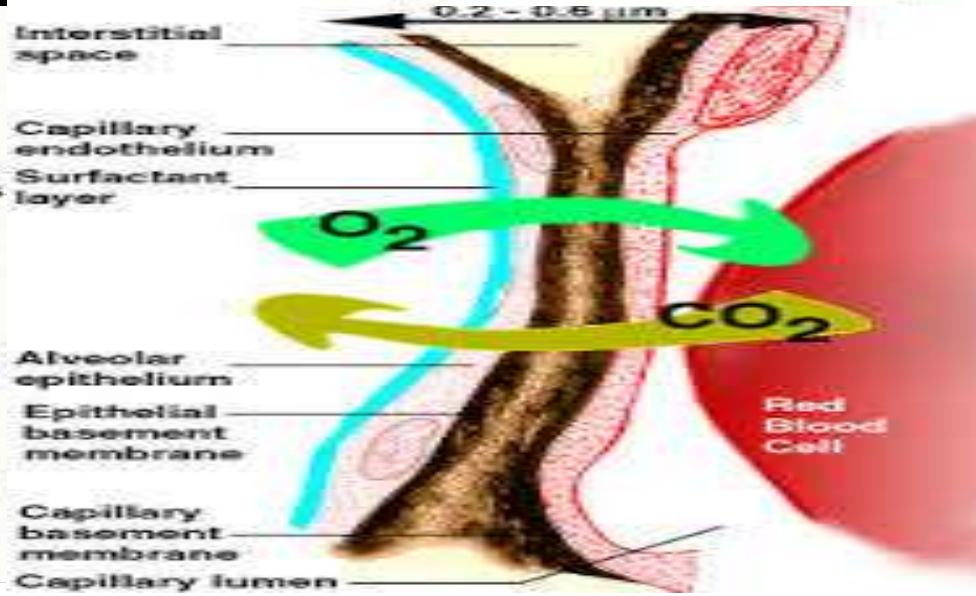
(Nephrology)

What do the lungs and kidneys have in common?









The basic pathology

- Focal proliferative glomerulonephritis.
- Fibrinoid necrosis is frequently seen.
- Microvascular thrombi.
- Extensive crescent formation.
- Interstitial infiltration, fibrosis and tubular atrophy are poor prognostic factors.
- Necrotizing granulomas and small-vessel vasculitis are rare findings.

Pulmonary-renal syndromes

Clinical entities classified according to the pathogenetic mechanism involved

Pulmonary-renal syndrome associated with anti-GBM antibodies: Goodpasture's syndrome

Pulmonary-renal syndrome in ANCA-positive systemic vasculitis

- Wegener's granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome
- Other vasculitis

Pulmonary-renal syndrome in ANCA-negative systemic vasculitis

- Henoch-Schönlein purpura
- Mixed cryoglobulinaemia
- Behçet's disease
- IgA nephropathy

ANCA-positive pulmonary-renal syndrome without systemic vasculitis: idiopathic pulmonary-renal syndrome

- Pauci-immune necrotic glomerulonephritis and pulmonary capillaritis

Pulmonary-renal syndrome in drug-associated ANCA-positive vasculitis

- Propylthiouracil
- D-Penicillamine
- Hydralazine
- Allopurinol
- Sulfasalazine

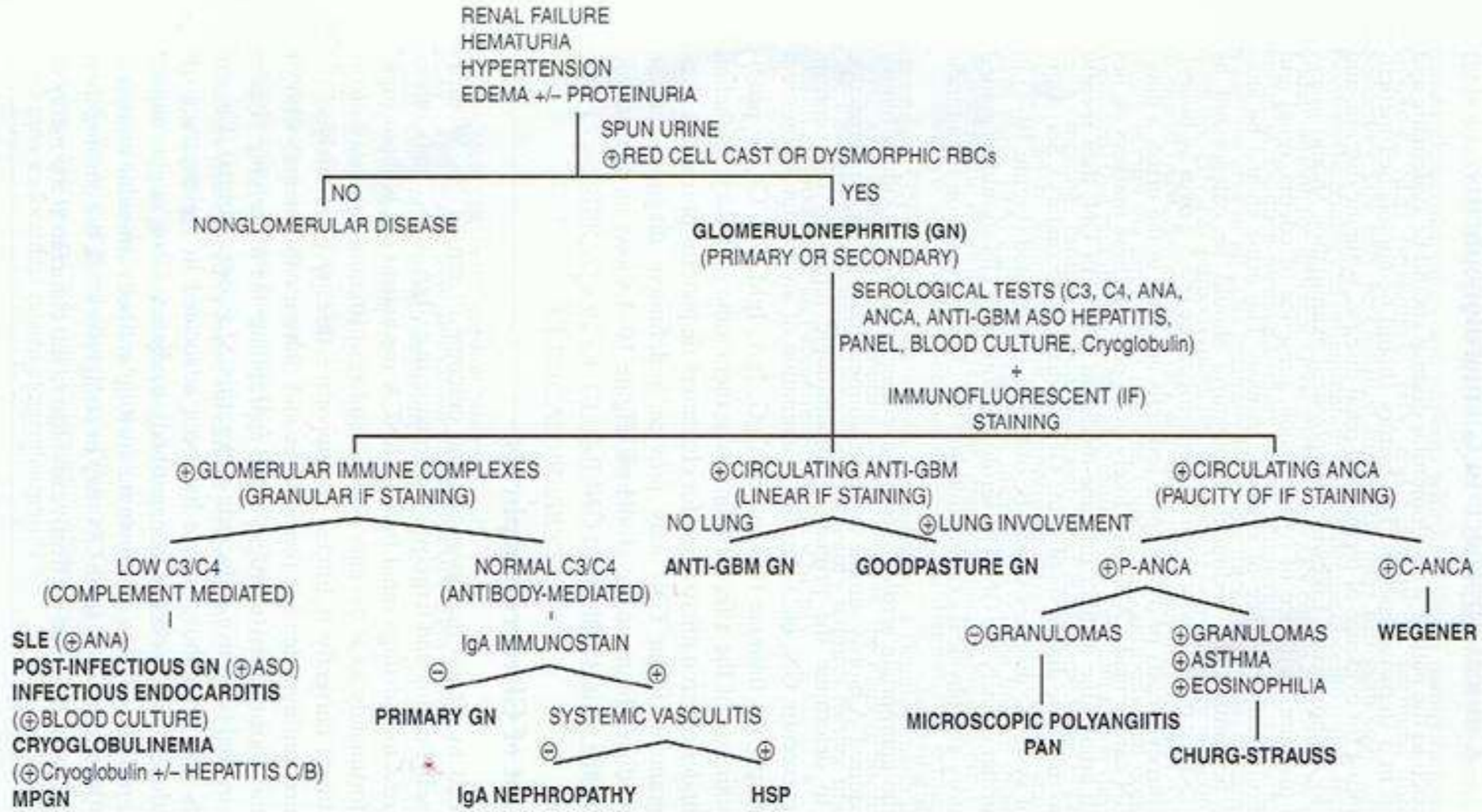
Pulmonary-renal syndrome in anti-GBM-postive and ANCA-positive patients

Pulmonary-renal syndrome in autoimmune rheumatic diseases (immune complexes and/or ANCA mediated)

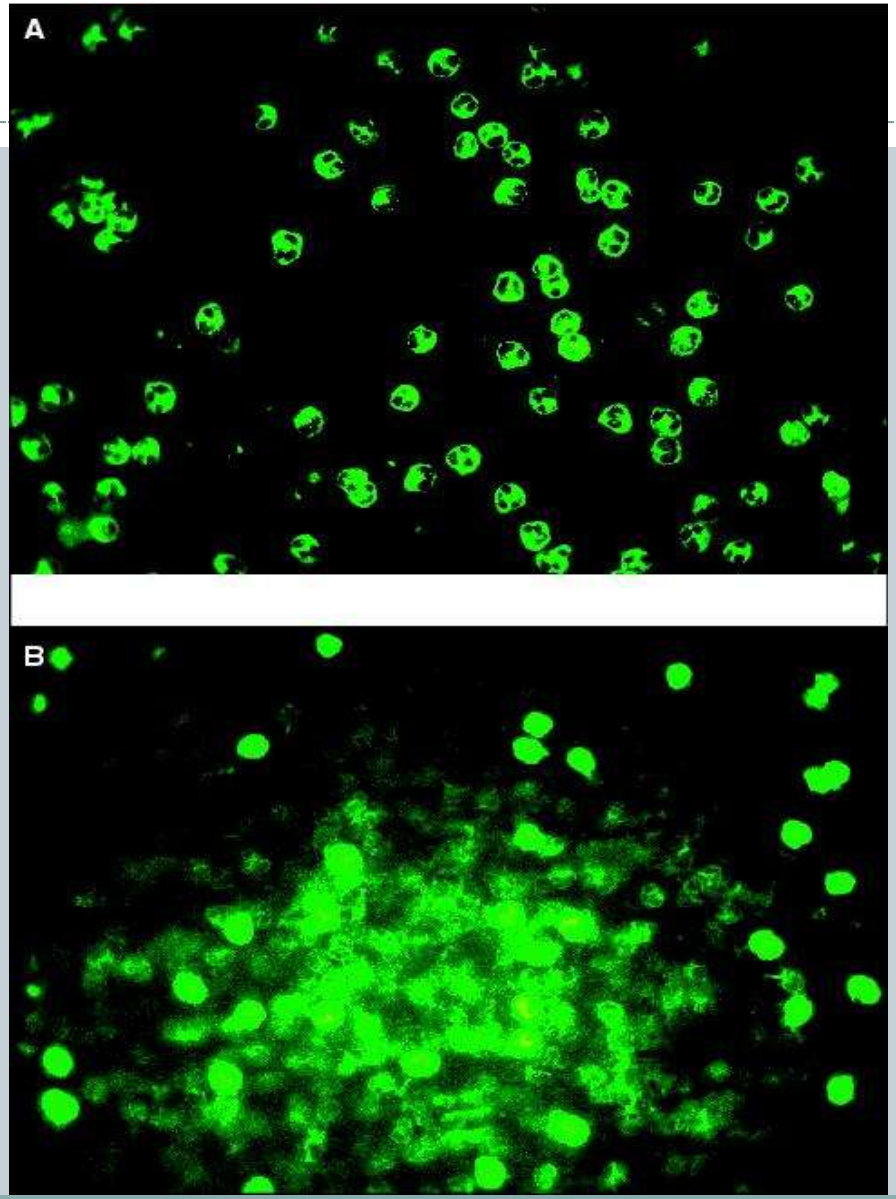
- Systemic lupus erythematosus
- Scleroderma (ANCA?)
- Polymyositis
- Rheumatoid arthritis
- Mixed collagen vascular disease

Pulmonary-renal syndrome in thrombotic microangiopathy

- Antiphospholipid syndrome
- Thrombotic thrombocytopenic purpura
- Infections
- Neoplasms

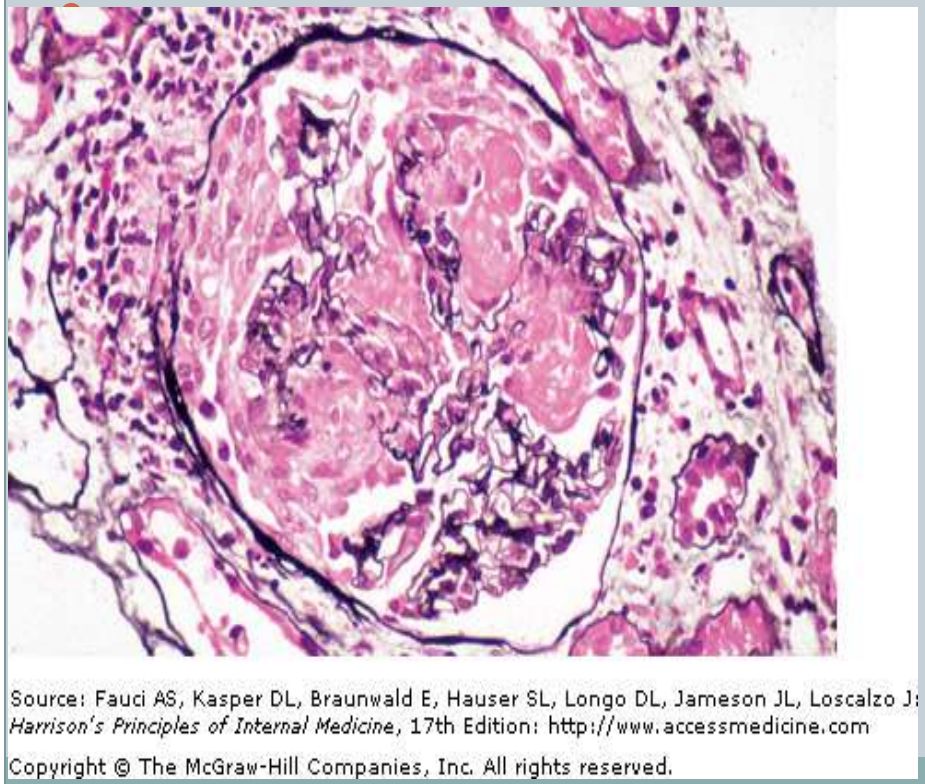

RENAL FAILURE
HEMATURIA
HYPERTENSION
EDEMA +/– PROTEINURIA
SPUN URINE
⊕RED CELL CAST OR DYSMORPHIC RBCs
NO
NONGLOMERULAR DISEASE
YES
GLOMERULONEPHRITIS (GN)
(PRIMARY OR SECONDARY)
SEROLOGICAL TESTS (C3, C4, ANA, ANCA, ANTI-GBM ASO HEPATITIS, PANEL, BLOOD CULTURE, Cryoglobulin)
+
IMMUNOFLUORESCENT (IF) STAINING
⊕GLOMERULAR IMMUNE COMPLEXES
(GRANULAR IF STAINING)
⊕CIRCULATING ANTI-GBM
(LINEAR IF STAINING)
⊕CIRCULATING ANCA
(PAUCITY OF IF STAINING)
NO LUNG
⊕LUNG INVOLVEMENT
LOW C3/C4
(COMPLEMENT MEDIATED)
NORMAL C3/C4
(ANTIBODY-MEDIATED)
ANTI-GBM GN
GOODPASTURE GN
⊕P-ANCA
⊕C-ANCA
SLE (⊕ANA)
POST-INFECTIOUS GN (⊕ASO)
INFECTIOUS ENDOCARDITIS
(⊕BLOOD CULTURE)
CRYOGLOBULINEMIA
(⊕Cryoglobulin +/– HEPATITIS C/B)
MPGN
IgA IMMUNOSTAIN
⊖
⊕
PRIMARY GN
SYSTEMIC VASCULITIS
⊖
⊕
IgA NEPHROPATHY
HSP
⊖GRANULOMAS
⊕GRANULOMAS
⊕ASTHMA
⊕EOSINOPHILIA
WEGENER
MICROSCOPIC POLYANGIITIS
PAN
CHURG-STRAUSS

C ANCA above P ANCA below

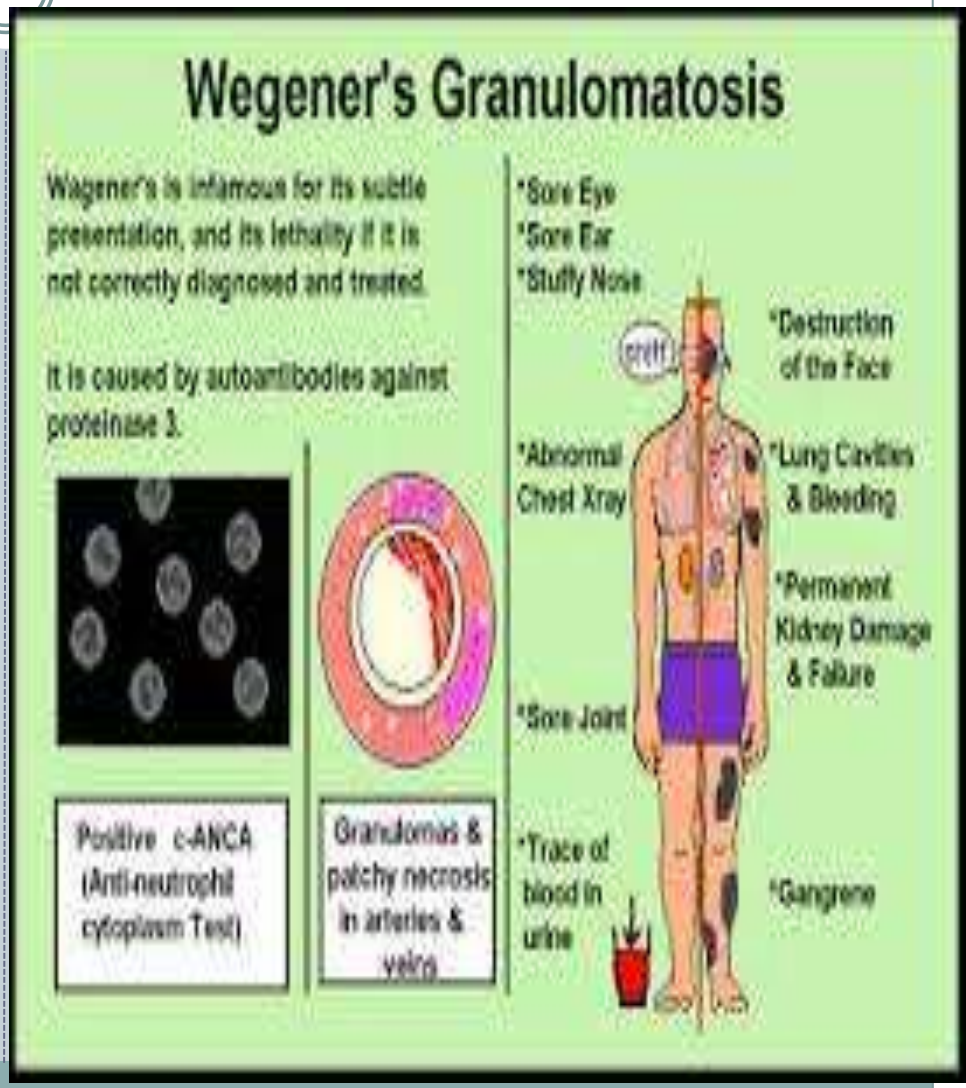


Wegener's Granulomatosis

- Necrotizing Vasculitis of SMALL VESSELS (arterioles AND veins) .



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com



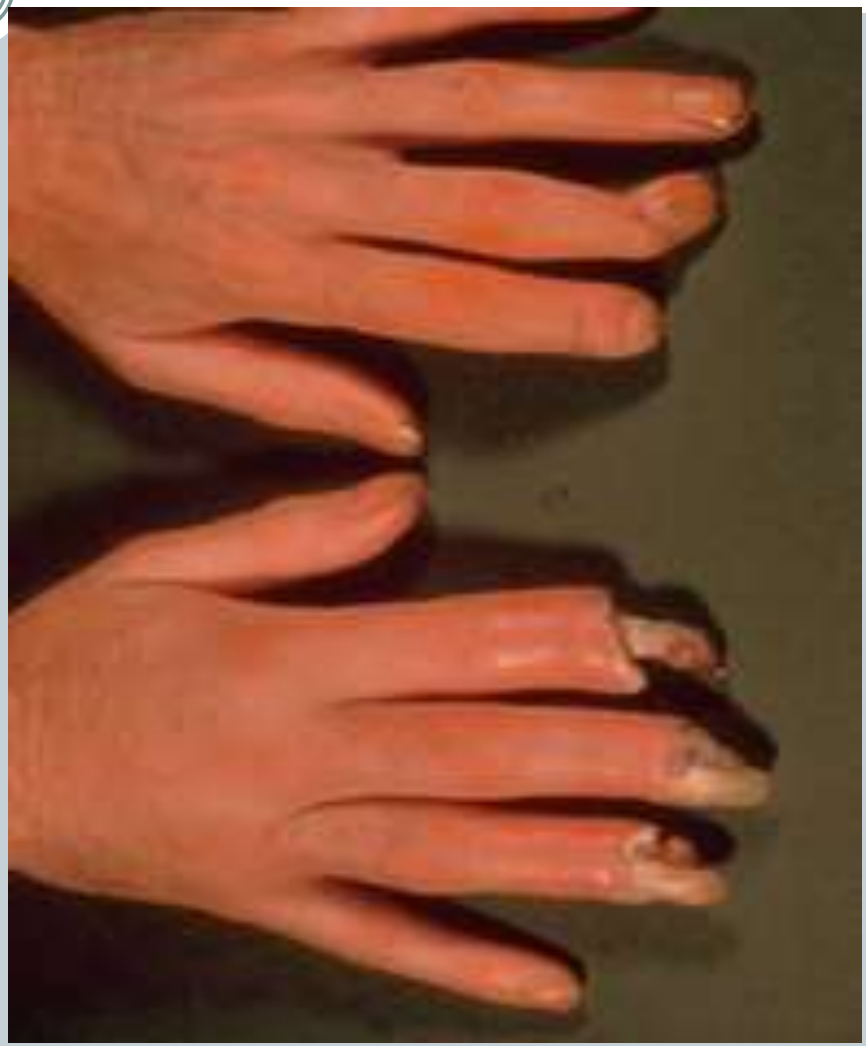
Wegener's Granulomatosis

- If no renal involvement it is called LMITED Wegeners – but kidneys usually get involved later.

- Lung biopsy has highest yield.
- More common in people with apha-1 antitrypsin deficiency → which inhibits PR3
- Rx: STEROIDS + CYCLOPHOSPHAMIDE .
- Plasmapharesis is not established - may or may not be used initially depending on severity
- 25% will relapse → REPEAT ABOVE TREATMENT and give Methotrexate OR Azathioprine to maintain remission.

Microscopic polyangitis

- Necrotizing vasculitis, glomerulonephritis, and pulmonary capilaritis.
- NO GRANULOMAS on biopsy.
- Lungs are involved only 50% of the time
- Can also cause GI vasculitis , cutaneous vasculitis and Mononeurtis complex.
- Rx: STEROIDS + IMMUNOSUPPRESSANT. Plasmapharesis is not established – may or may not be used depending on severity.
- Relapse also occurs – 35% of the time – treated the same – repeat and give maintenance therapy with MTX or Azathioprine



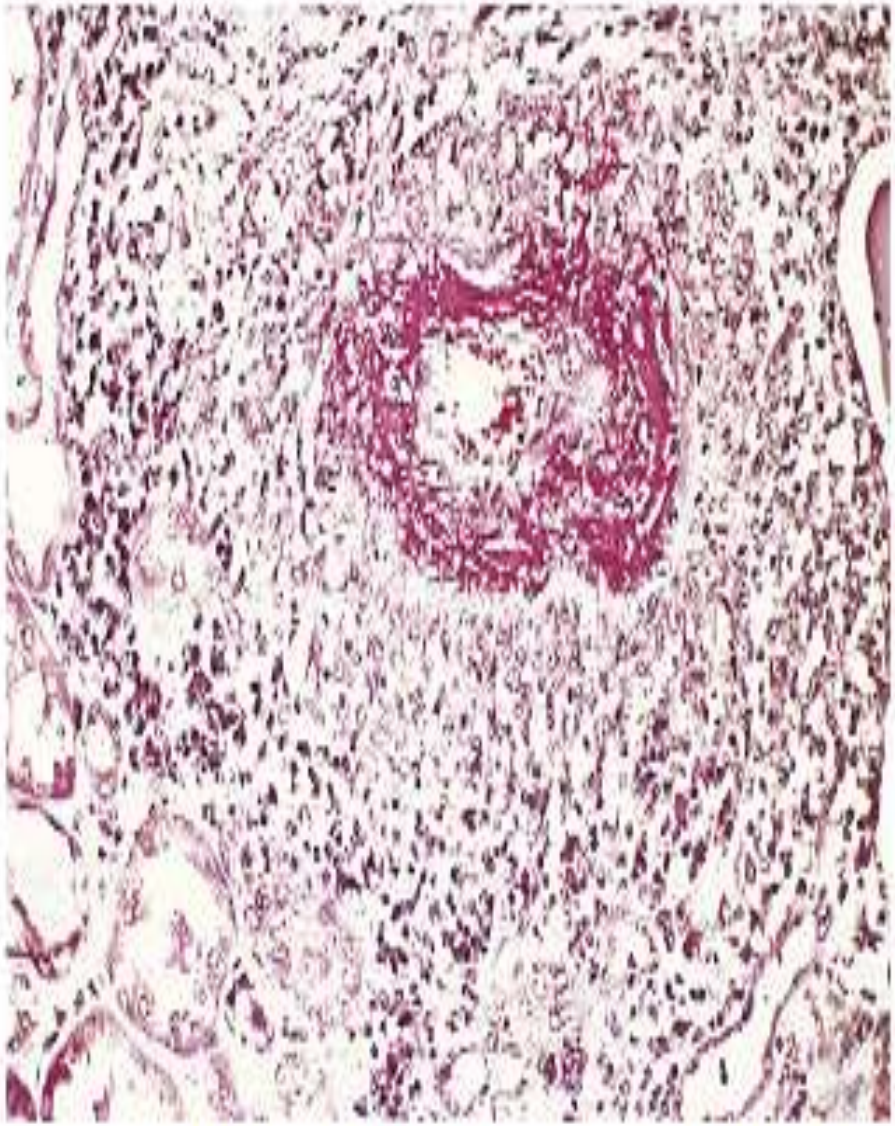
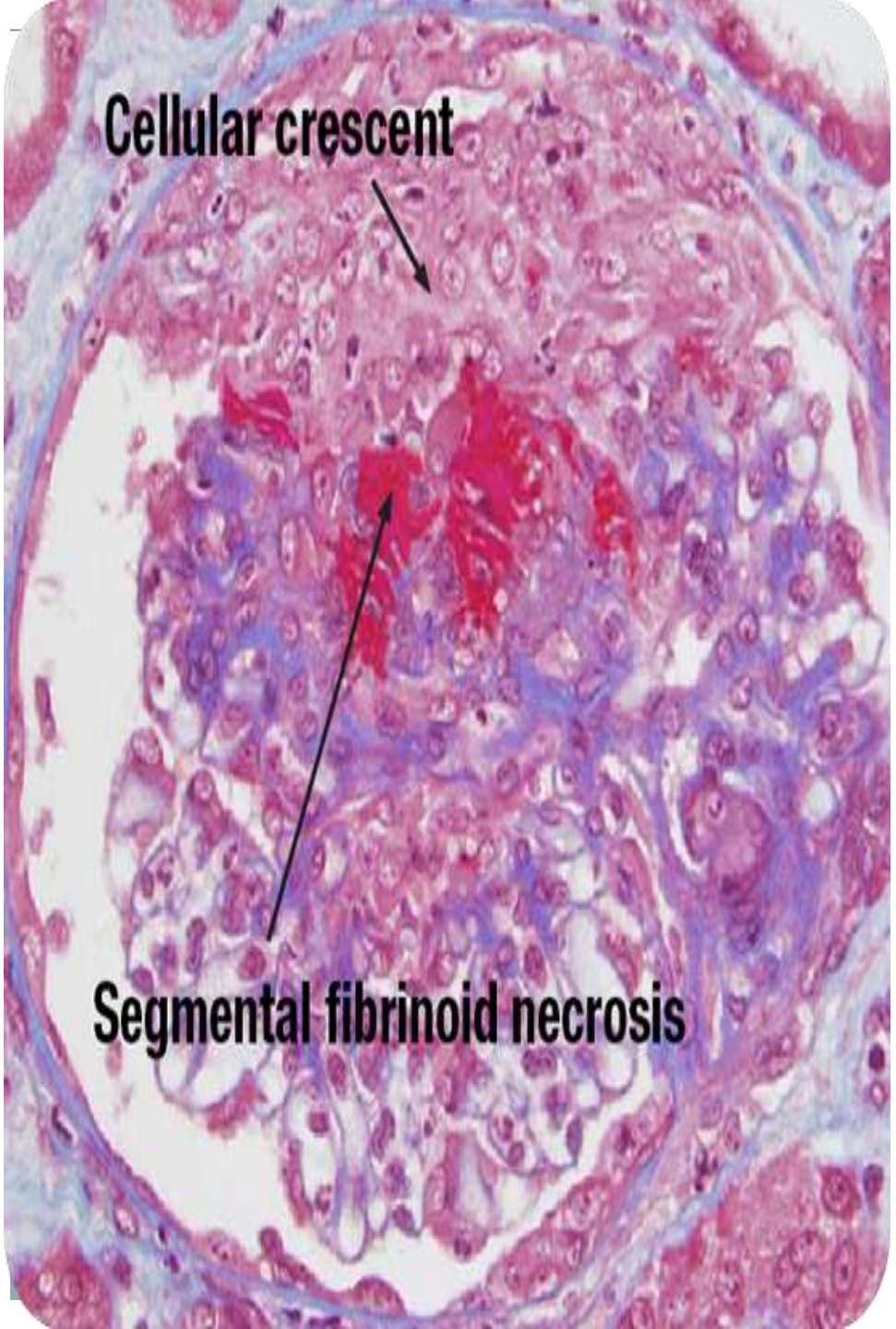


Figure 23.2 Renal interlobular artery with fibrinoid necrosis from a patient with microscopic polyangiitis (Masson trichrome stain).



Churg Strauss Syndrome

- Small vessel vasculitis with focal segmental necrotizing GN.
- Rare “allergic state” with systemic inflammation associated with Asthma, Hypergammaglobulinemia, RF+, raised IgE levels, and EOSINOPHILS
- Symptoms: Lung involvement dominates and may preceded others by years: Cough, infiltrates, severe asthma, 1/3 have pleural effusions – high in eosinophils.
- GN (45%), Rhinitis, mononeuritis, Skin involvement (50%) , GI vasculitis and Cardiovascular inflammation resulting in MI (most frequent cause of death in Churg Strauss)

Churg Strauss….

- Kidney biopsy usually does not show granuloma or eosinophils (granulomas and eosinophils are present in lung and elsewhere) . Do blood tests for IgE, Eosinophils.

- Rx: similar: STEROIDS + IMMUNOSUPRESSANTS

Goodpasture's syndrome

- Autoimmune disease with Abs against the "α 3 NC1 domain of TYPE IV COLLAGEN" on the basement membrane.
- This epitope becomes 'exposed' by infections,lithotripsy, smoking, solvents, and oxidants
  - 10-15% also have p-ANCA abs against Myeloperoxidase (MPO) – a vasculitis variant which has good prognosis.
- Genetics: HLA DR2, DQ

Goodpastures syndrome…

- Bimodal Age distribution:
  - Men in late 20s
  - Men and women 60-70s

Young Men in 20s:

- Explosive, sudden onset.
- Sudden anemia
- More lung involvement than in older age group
- Hemoptysis - specially if smokers
- Dyspnea,
- Hematuria
- Better prognosis than older age group

Older Age Group: 60-70s , M and F

- Prolonged asymptomatic renal injury
- May present with oliguria – Poor prognosis
- Lung disease may range from mild dyspnea to outright pulmonary hemorrhage
- Urgent kidney biopsy if we suspect this disease and there are mild or no lung signs

Goodpasture's syndrome…

DIAGNOSIS:

Renal Biopsy:

– Focal (<50% glomeruli affected)

- or segmental (glomeruli tuft involved in segments)

Linear Immunoflorescence staining
Anti GBM Abs against α3 -NC1-Collagen IV

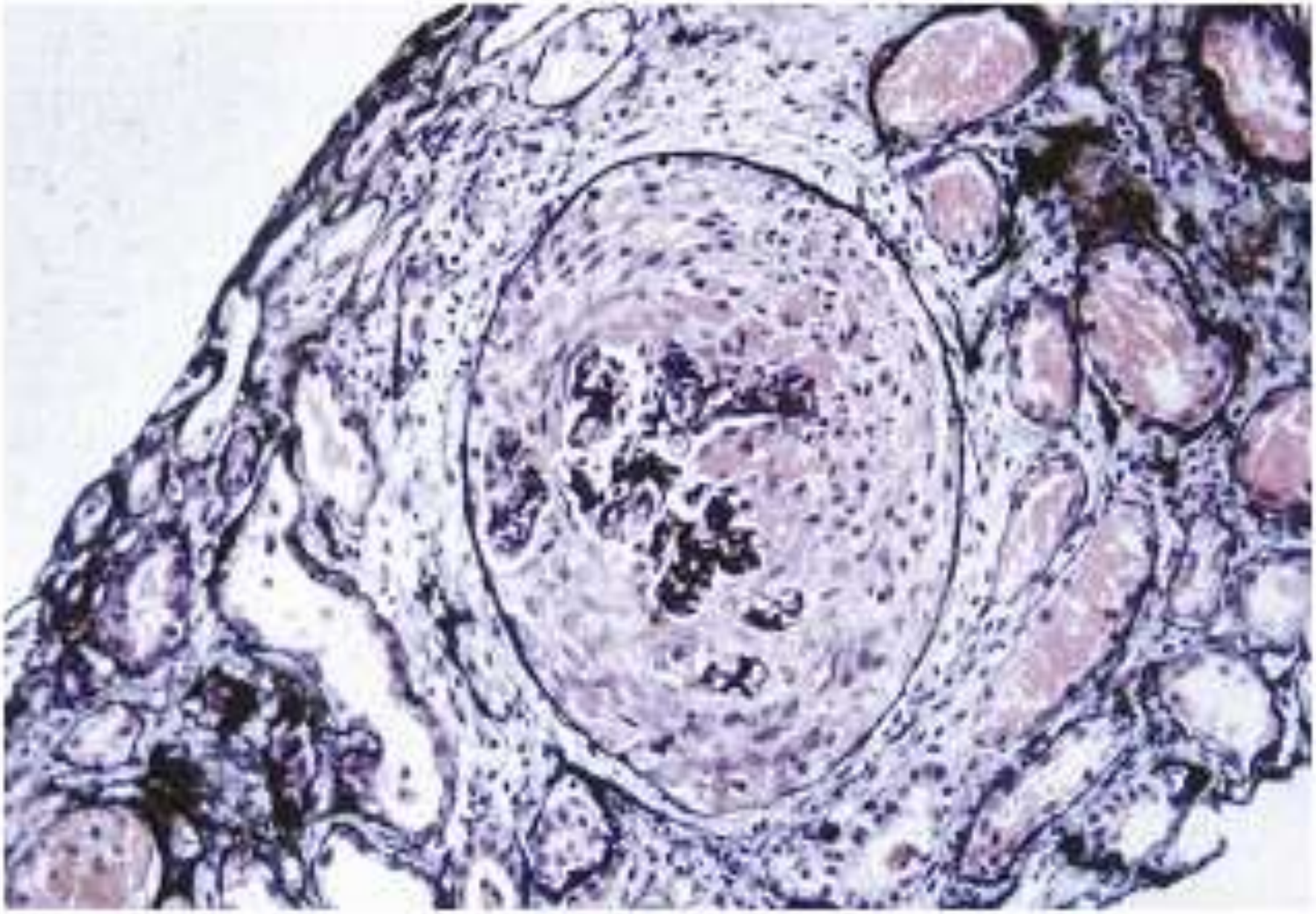
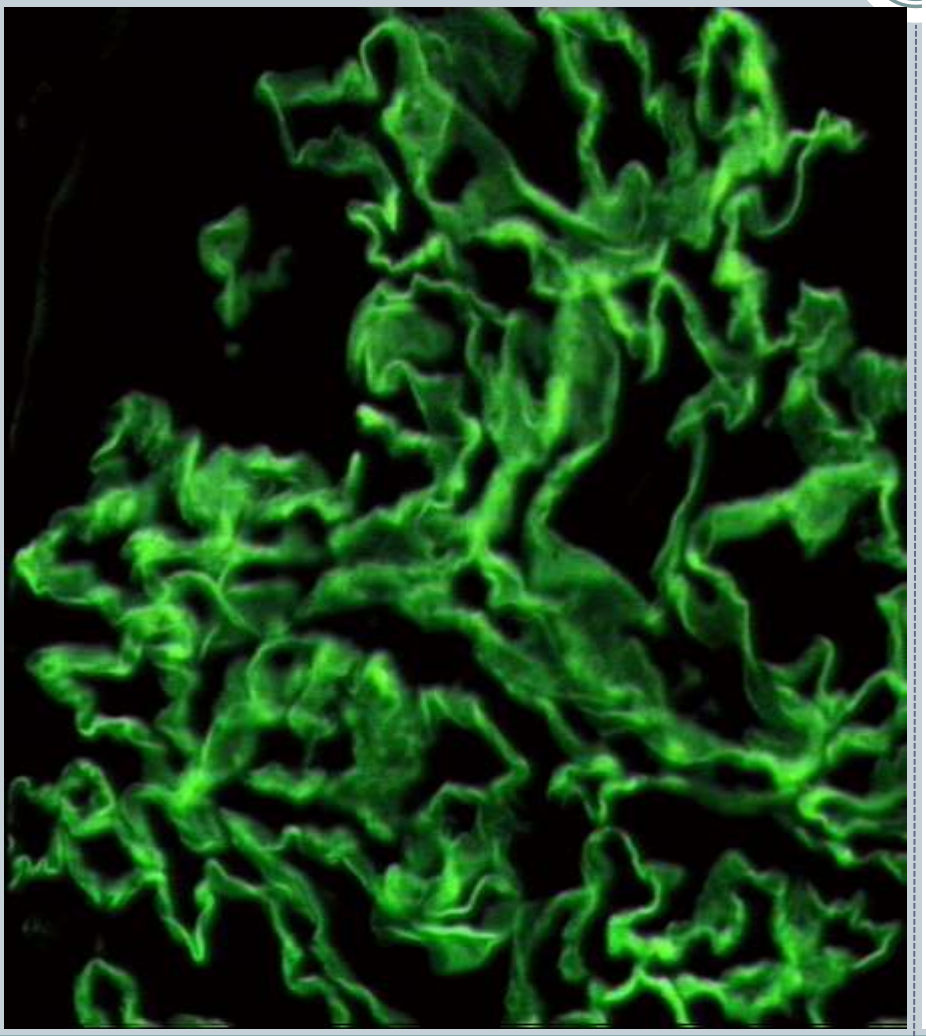


Figure 21.2 Renal biopsy from a patient with Goodpasture disease showing acute crescentic glomerulonephritis *(silver stain)*.

Goodpasture's: Linear immunoflorence



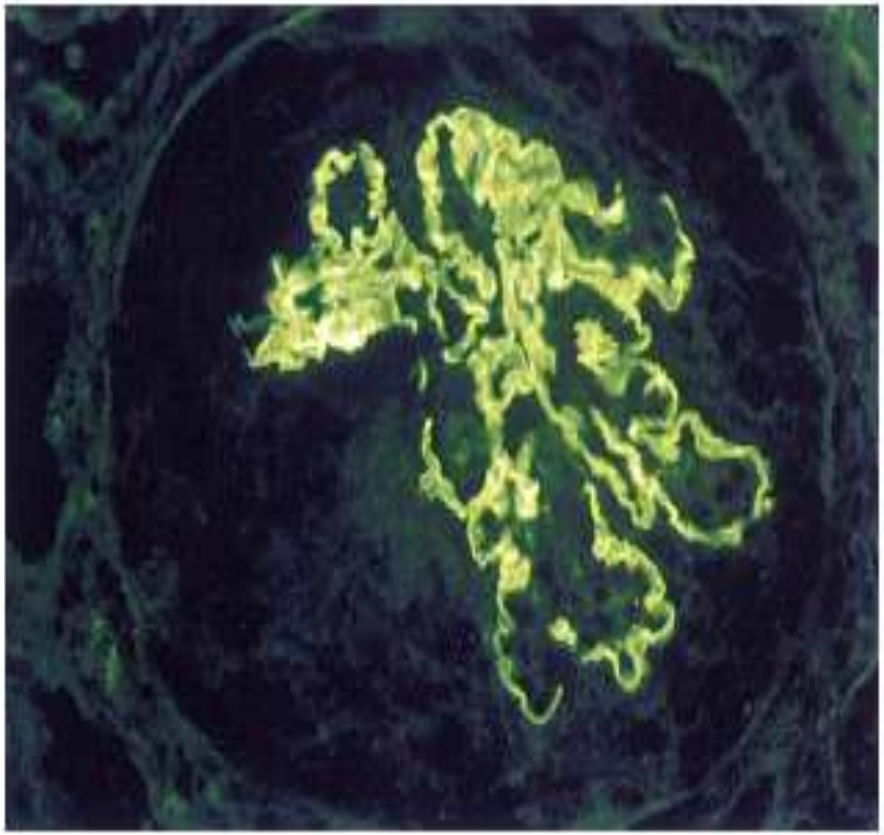


Figure 21.3 Renal biopsy from a patient with Goodpasture disease. Immunofluorescence microscopy shows linear deposition of immunoglobulin G along the glomerular basement membrane.

Table 21.1 Initial Treatment of Goodpasture Disease

Plasma exchange	Daily 4-L exchange for 5% human albumin solution. Use 300-600 mL fresh plasma within 3 days after invasive procedure (e.g., biopsy) or in patients with pulmonary hemorrhage. Continue for 14 days or until antibody levels are fully suppressed. Withhold if platelet count is <70,000/μL, fibrinogen <1 g/L or hemoglobin is <9 g/dl. Watch for coagulopathy, hypocalcemia, and hypokalemia.
Cyclophosphamide	Daily oral dosing at 2-3 mg/kg/day (round down to nearest 50 mg; use 2 mg/kg/day in patients >55 years). Stop if white cell count is $<4 \times 10^3$/mL, and restart at lower dose when count increases to $>4 \times 10^3$/mL. Pulsed IV cyclophosphamide has not been tested formally, but is equivalent in ANCA associated vasculitis.
Prednisone	Daily oral dosing at 1 mg/kg/day (maximum, 60 mg). Reduce dose weekly to 20 mg by week 6, and then more slowly. There is no evidence of benefit of IV methylprednisolone, and it may increase infection risk (possibly use it if plasma exchange not available).
Prophylactic treatments	Use oral nystatin and amphotericin (or fluconazole) for oropharyngeal fungal infection. Use histamine 2 blocker or proton-pump inhibitor for steroid-promoted gastric ulceration. Use low-dose cotrimoxazole for PCP.

Goodpasture's syndrome

Signs of Poor Prognosis:

- Biopsy shows >50% crescent and advanced fibrosis, (specially seen in long standing asymptomatic disease in older pts.)
- Cr> 6.8 mg/dl
- Oliguria
- If needs urgent dialysis at presntation → may not even respond to plasmapheresis or steroids

Goodpasture's … treatment and prognosis

- Even if kidney disease does not respond to plasmapharesis – lung disease does and it can be lifesaving.
- Kidney transplant can be considered – but wait 6 months for antibodies to clear out.
- Disease recurs in transplanted Alport pt. (they lack α3,α5 chain).

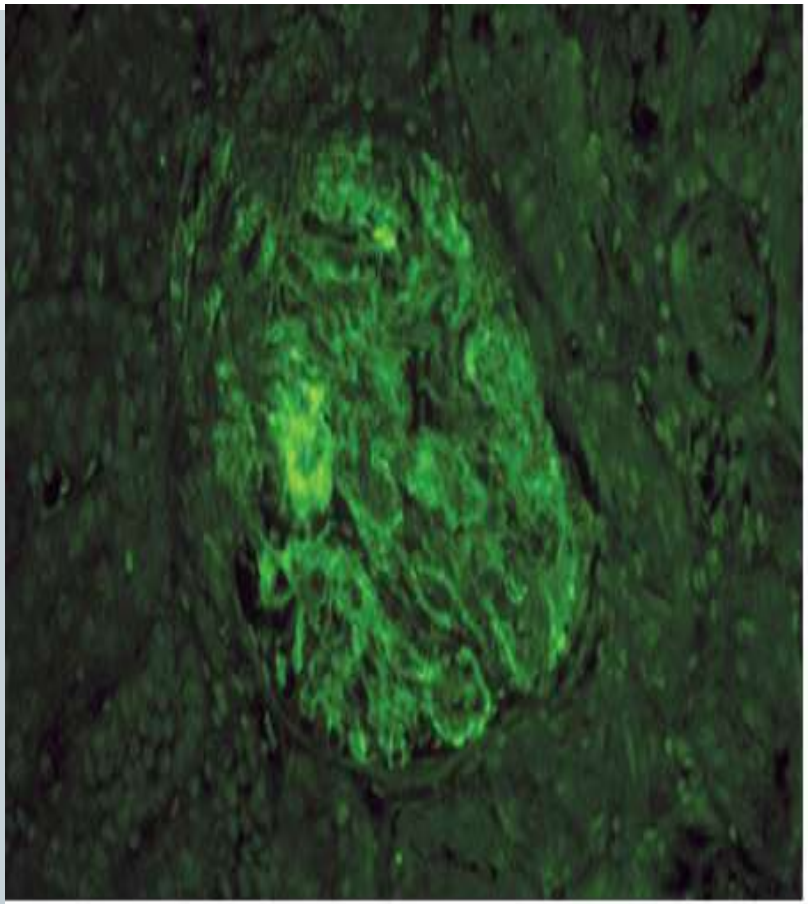
Dr Goodpasture, 1919

Lupus Nephritis ....

Classification of SLE with Reference to Glumerulonephritis

Class	Renal Histology (type of lupus nephritis)	Prognosis for Renal Function
I	Minimal mesangial	Excellent
II	Mesangial proliferative	Good
III	Focal	Moderate
IV	Diffuse	Moderate-Poor
V	Membranous	Moderate
VI	Advanced sclerosing	Poor

Lupus Nephritis



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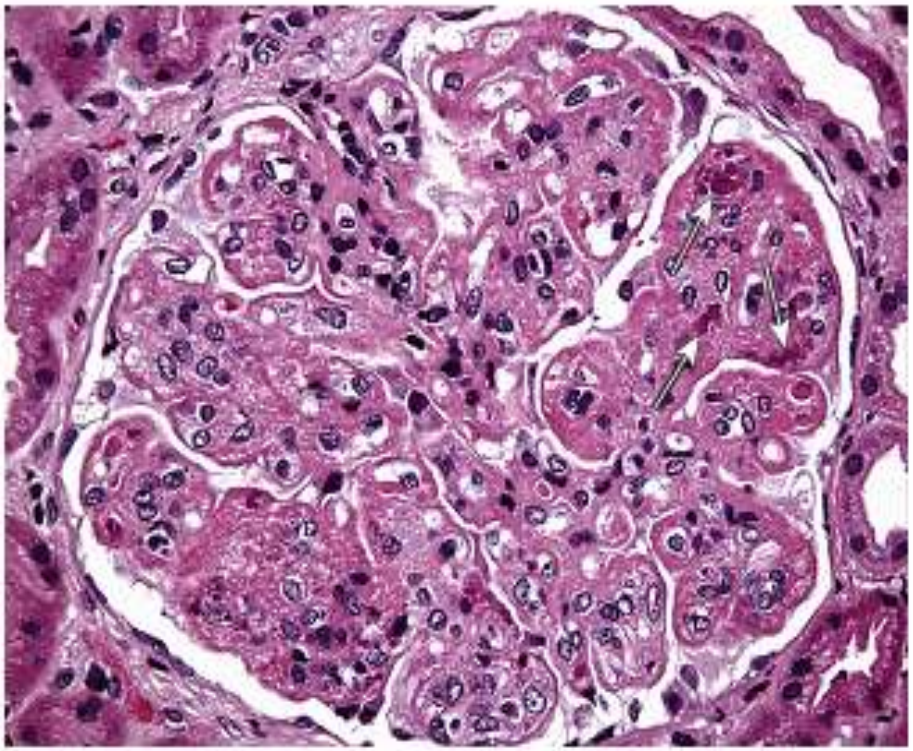


Figure 24.2 Class IV lupus nephritis: A representative glomerulus shows global narrowing or obliteration of its capillary lumina by endocapillary proliferation, including infiltrating leukocytes. The glomerular capillary walls are thickened by eosinophilic material, forming wire loops. Rounded basophilic structures ("hematoxylin bodies," *arrows*) represent extruded nuclei altered by binding to antinuclear antibody. (Hematoxylin and eosin, ×400).

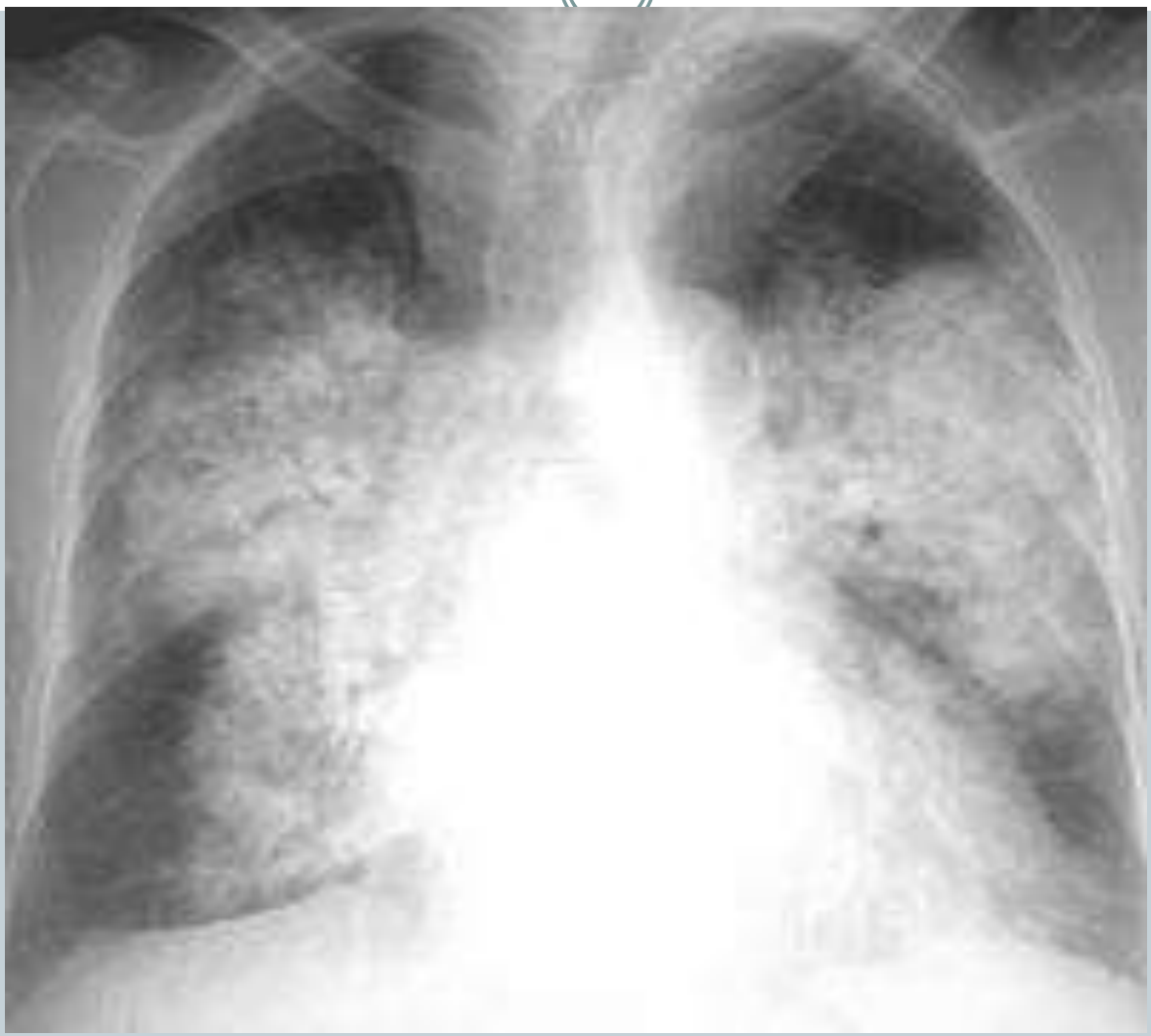
Table 24.3 Treatment Options for Lupus Nephritis, Stratified by International Society of Nephrology Classification and Phase of Therapy

Class	Induction Phase	Maintenance Phase
Class I* Class II	Conservative, nonimmunomodulatory therapy (e.g., RAAS blockade)	Conservative, nonimmunomodulatory therapy (e.g., RAAS blockade)
Class III* Class IV	Pulse IV steroids followed by tapering doses of oral steroids *and* IV cyclophosphamide 0.75-1.0 g/m² IV monthly for 6 doses *or* IV cyclophosphamide 500 mg IV every 2 wk for 6 doses *or* MMF 2000-3000 mg/day for 6 mo	Lowest tolerable amount of oral steroids *and* MMF 2000 mg/day for 6 mo, then 1500 mg/day for 3-6 mo, then 1000 mg/day afterward assuming stable disease *or* Azathioprine 2.0 mg/kg/day for 6 mo, then 1.5 mg/kg/day for 3-6 mo, then 1.0 mg/kg/day afterward assuming stable disease
Class V	Pulse IV steroids followed by tapering doses of oral steroids *and* IV cyclophosphamide 0.75-1.0 g/m² IV monthly for 6 doses *or* Cyclosporine (dose adjusted to goal trough level 125-200 mcg/L) *or* Tacrolimus (dose adjusted to goal trough level 5-10 mcg/L) *or* MMF 2000-3000 mg/day for 6 mo	Lowest tolerable amount of oral steroids *and* MMF 2000 mg/day for 6 mo, then 1500 mg/day for 3-6 mo, then 1000 mg/day afterward assuming stable disease *or* Azathioprine 2.0 mg/kg/day for 6 mo, then 1.5 mg/kg/day for 3-6 mo, then 1.0 mg/kg/day afterward assuming stable disease
Class VI	Conservative, nonimmunomodulatory therapy (e.g., RAAS blockade) with preparation for kidney replacement therapy	Not applicable

Uremic Lung / Uremic Pulmonary Edema

- Occurs in severe renal failure, ESRD , specially when HTN also present.
- There is increase in pulmonary capillary permeability due to uremia effects – causing protein rich fluid to enter the lungs from the capillaries – causes Uremic Pulmonary Edema.
- CXR shows perihilar edema, though peripheries are clear.
- DIALYSIS

Bat-Wing lung



Post-Infectious GN

Table 22.1 Infectious Agents Most Frequently Associated With Glomerulonephritis

Bacteria	Viruses
Streptococcus	Hepatitis B
Staphylococcus	Hepatitis C
Pneumococcus	Echovirus
Enterobacteriaceae	Adenovirus
Salmonella typhi	Coxsackievirus
Meningococcus	Cytomegalovirus
Treponema pallidum	Epstein-Barr virus
Brucella	Enteroviruses
Leptospira	Measles
Yersinia	Mumps
Rickettsia	Varicella
Legionella	Rubella

A 2008 American study identified bacteria causing glomerulonephritis were more frequently *Staphylococcus* (46%), *Streptococcus* (16%), and gram-negative organisms. The most common sites of infection were the upper respiratory tract (23%), skin (17%), lung (17%), and heart valves (11.6%). Chronic glomerulonephritis developed in 25% of patients.

Post-Infectious GN

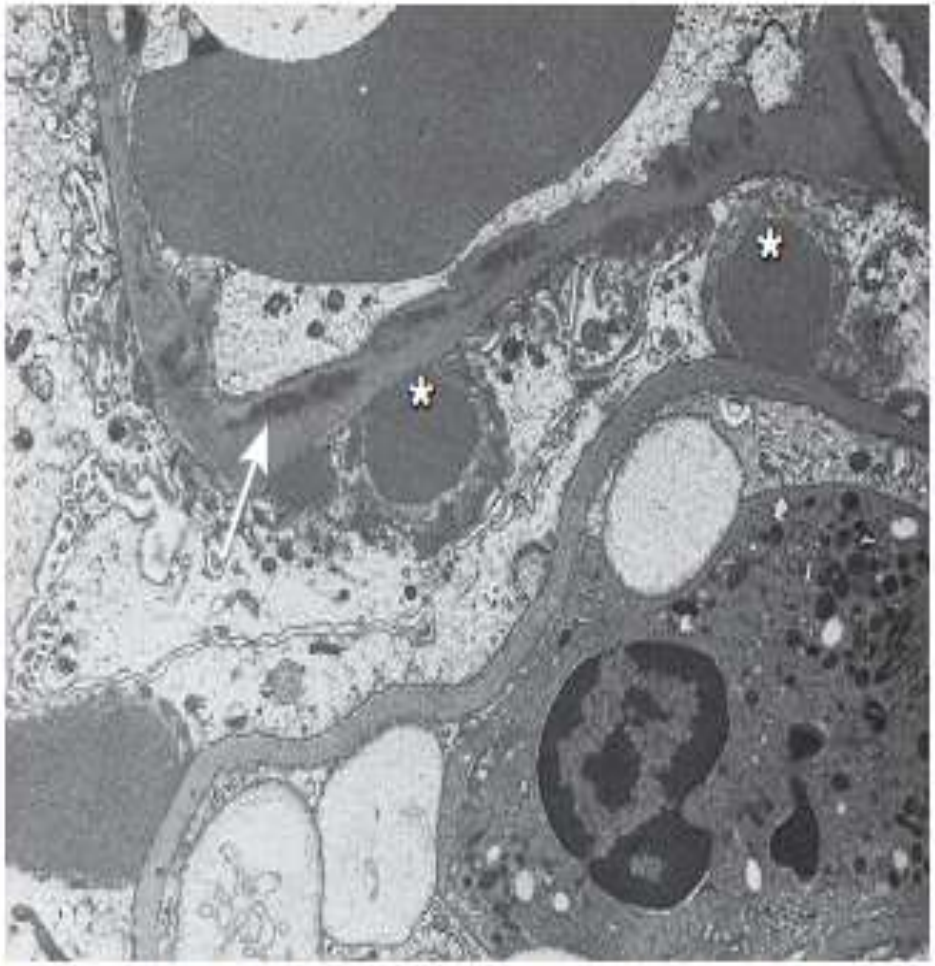


Figure 22.3 Acute poststreptococcal glomerulonephritis. Electron microscopy discloses typical humps *(asterisks)* and intramembranous immune complexes *(arrow)*.

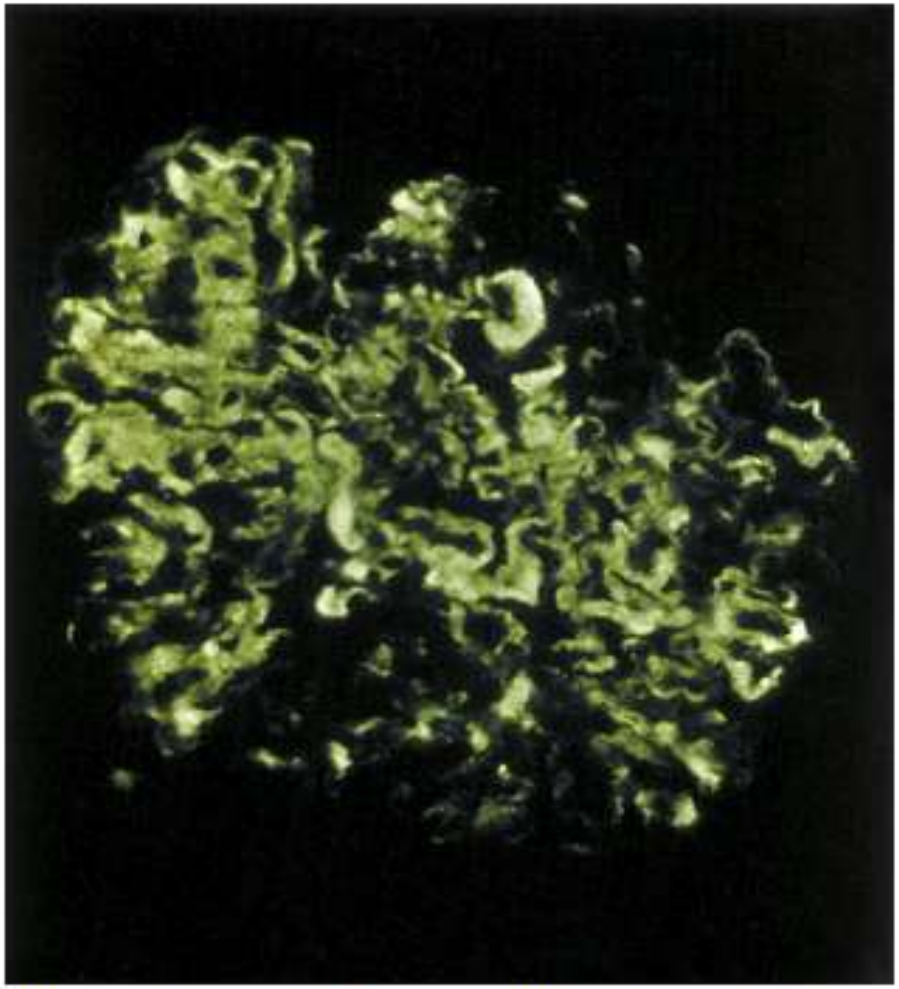


Figure 22.4 Acute poststreptococcal glomerulonephritis. Immunofluorescence with an anti-C3 antiserum discloses widespread "garland-type" C3 labeling, mostly along the glomerular basement membranes.

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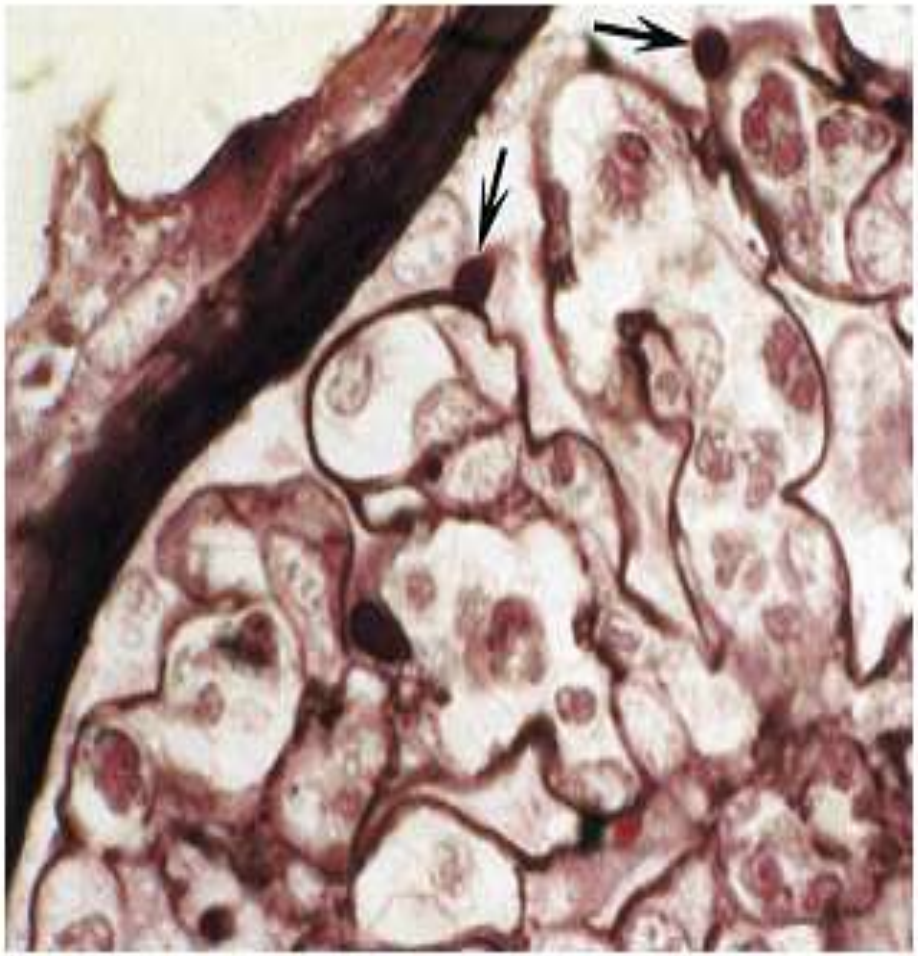


Figure 22.2 **Acute poststaphylococcal glomerulonephritis.** Typical humps on the outer aspect of the glomerular basement membranes *(arrows)*. Silver methenamine staining was used.

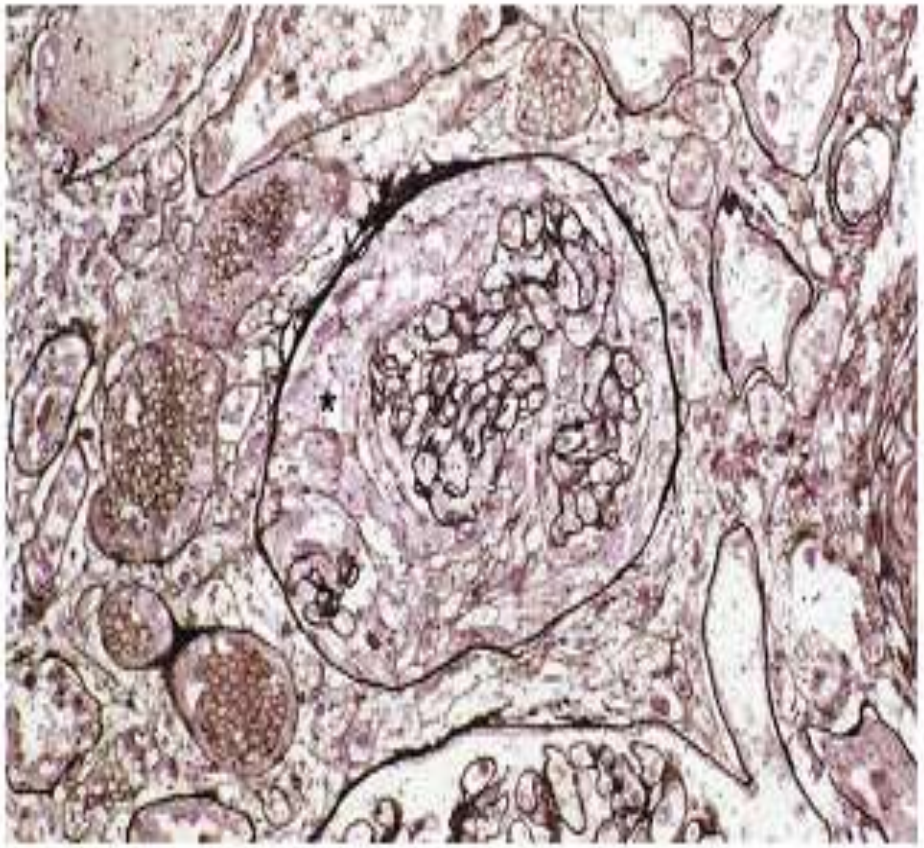
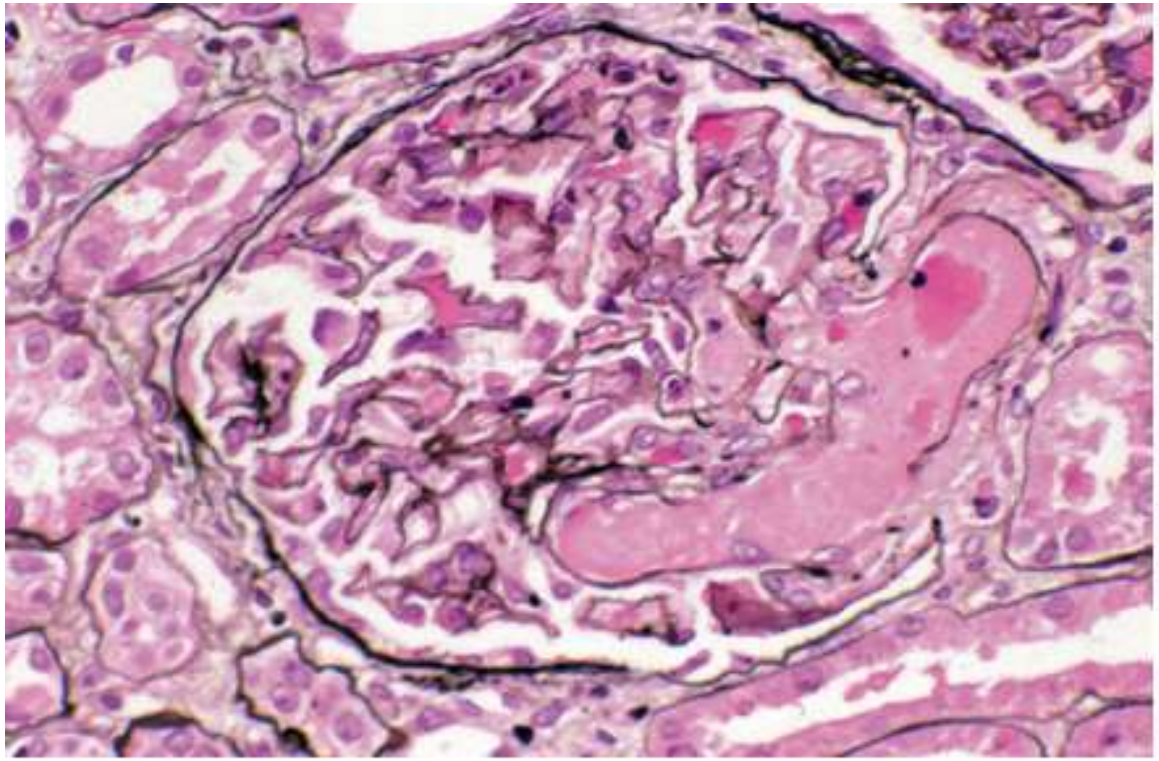


Figure 22.5 **Crescentic glomerulonephritis complicating a case of bacterial endocarditis in an elderly patient with urinary tract infection due to *Enterococcus faecalis*.** A circumferential crescent *(asterisk)* surrounds the remaining glomerular tuft. Silver methenamine staining was used.

Poor prognostic criteria

- Poor general health because of malnutrition or cirrhosis.
- Patients with septicemia and those whose sites of infection include visceral abscesses, empyema, meningitis, or endocarditis .
- Older patients and in those with purpura.
- Initial presentation with nephrotic syndrome, a serum creatinine above ~2.7 mg/dl.
- The presence of crescents and interstitial fibrosis on kidney biopsy .
- Persistently low serum complement .

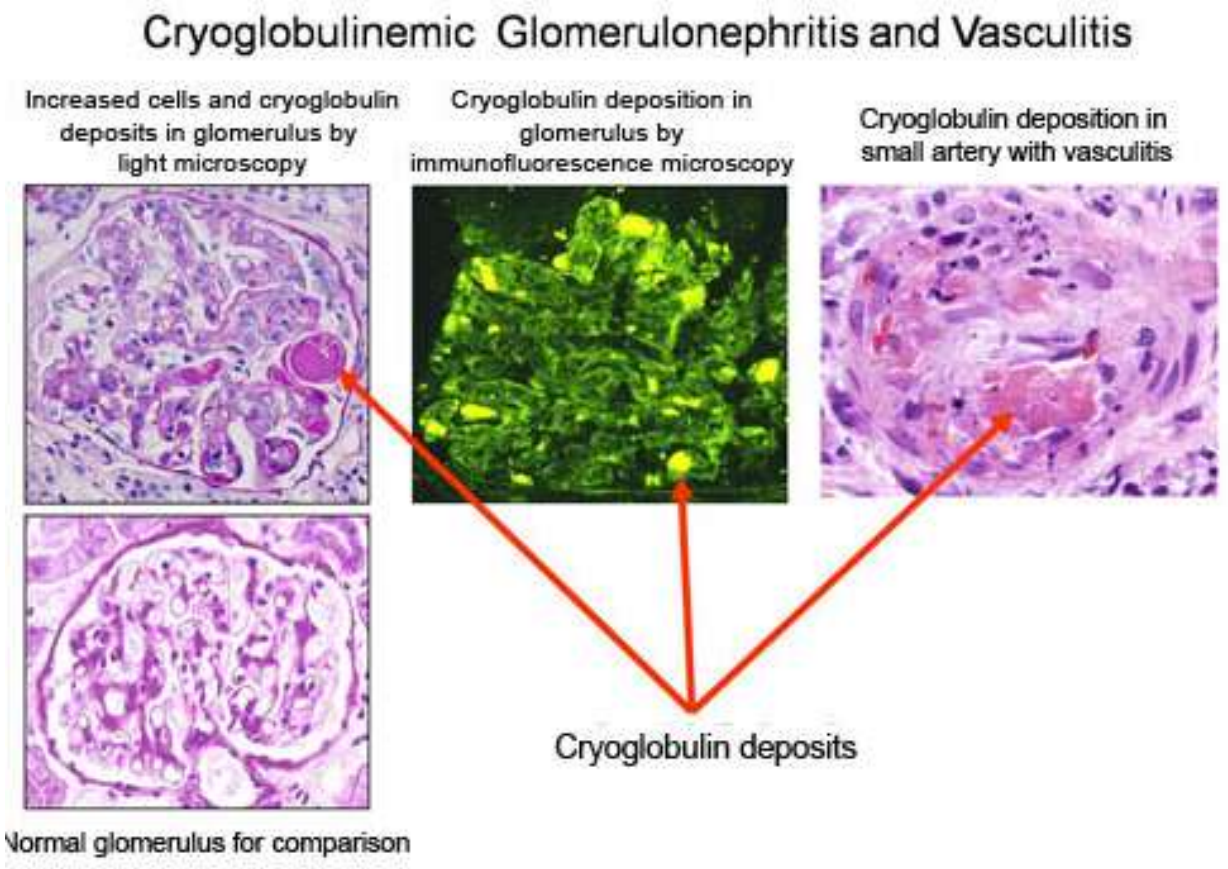
There are characteristic intraglomerular fibrin thrombi, with a chunky pink appearance. The remaining portion of the capillary tuft shows corrugation of the glomerular basement membrane due to ischemia.



Hemolytic Uremic Syndrome

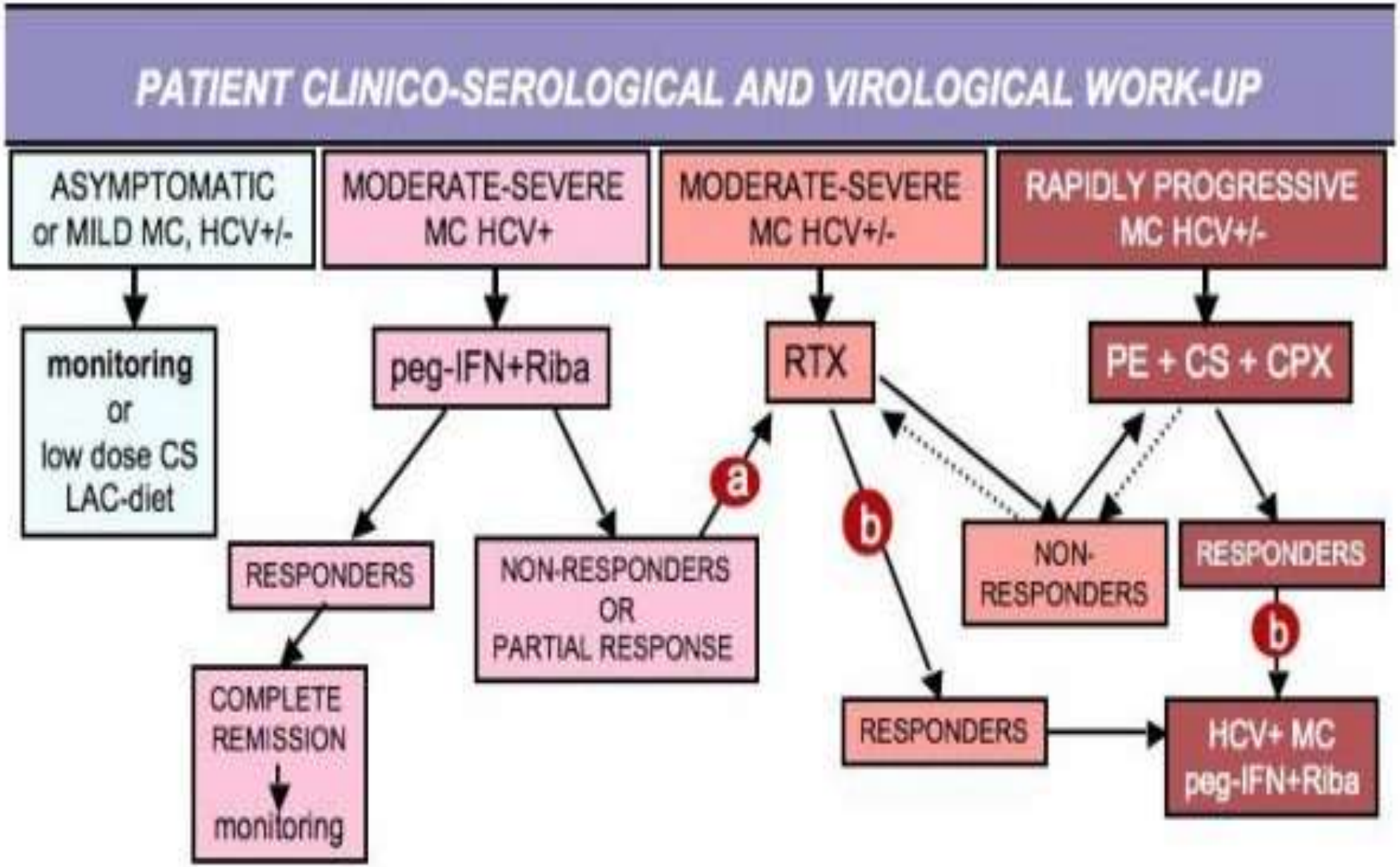
Type I is the result of a monoclonal Ig, usually (IgM) or, less frequently, (IgG), (IgA), or light chains.

Types II and III(mixed cryoglobulinemia) contain rheumatoid factors (RFs), which are usually IgM and, rarely, IgG or IgA. These RFs form complexes with the (Fc) portion of polyclonal IgG. The actual RF may be monoclonal (in type II) or polyclonal (in type III) Ig.



Cryoglobulinemia

THERAPEUTIC STRATEGIES OF MIXED CRYOGLOBULINEMIA SYNDROME (3)



IgA nephropathy

- Presentations:

1. Episodic gross hematuria
2. Asymptomatic microscopic hematuria
3. Nephrotic syndrome
4. AKI
5. Other: HTN-CKD

IgA nephropathy(HSP)

Table 20.1 Oxford Classification of Immunoglobulin A Nephropathy

Histologic Variable	Definition	Score
Mesangial hypercellularity	Mesangial hypercellularity score defined by the proportion of glomeruli with mesangial hypercellularity	M0 ≤0.5 M1 >0.5
Endocapillary hypercellularity	Hypercellularity because of increased number of cells within glomerular capillary lumina, causing narrowing of the lumina	E0 absent E1 present
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 absent S1 present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	T0 0% to 25% T1 26% to 50% T2 >50%

Note: Scoring should be assessed on period acid-Schiff-stained sections.

IgA nephropathy(HSP)

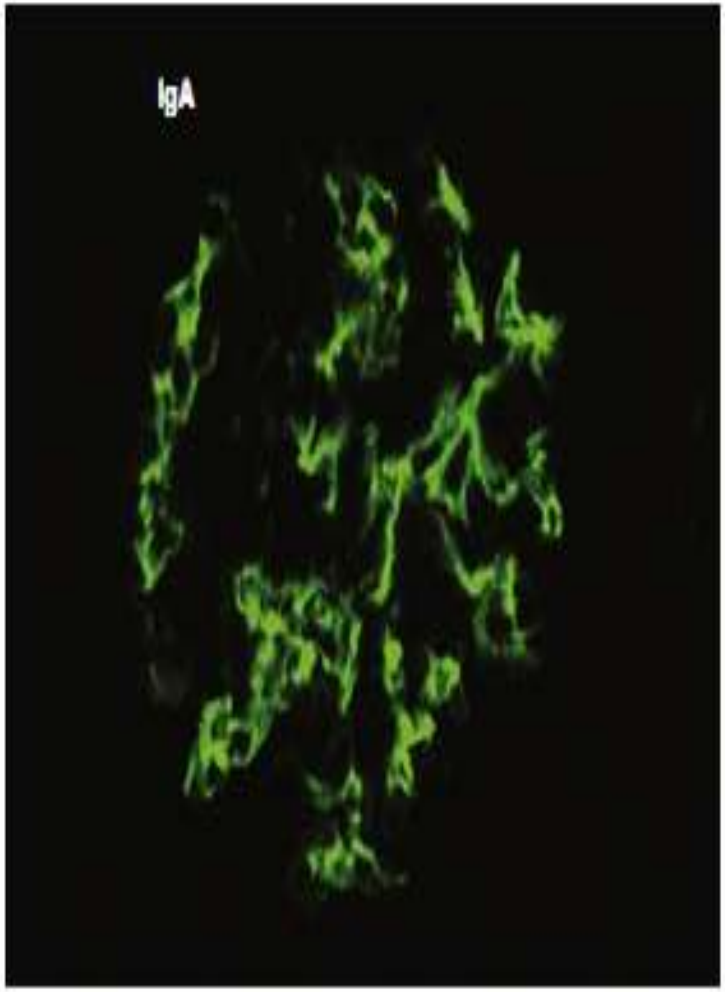


Figure 20.2 Kidney biopsy showing immunofluorescent staining for mesangial immunoglobulin A.

Table 20.3 Treatment Recommendations for Immunoglobulin A Nephropathy According to Clinical Features

Clinical Presentation	Recommended Treatment
Recurrent gross hematuria	No specific treatment—no role for antibiotics or tonsillectomy
Proteinuria <0.5 g/24 h ± microscopic hematuria	No specific treatment—no role for tonsillectomy
Proteinuria >0.5 g/24 h ± microscopic hematuria	Step 1: Maximally tolerated renin-angiotensin blockade with ACE inhibitor and/or ARB Step 2: If proteinuria remains >0.5 g/24 h, then consider immunosuppression Little convincing evidence for any particular agent but options include: Fish oil Corticosteroids Mycophenolate mofetil
Acute kidney injury	
Acute tubular necrosis	Supportive measures for acute tubular necrosis
Crescentic IgAN (with little or no chronic damage)	Induction (~8 weeks) Prednisolone 0.5 to 1 mg/kg/day Cyclophosphamide 2 mg/kg/day Maintenance Prednisolone in reducing dosage Azathioprine 2.5 mg/kg/day
Nephrotic syndrome	
With minimal change on light microscopy	Prednisolone 0.5 to 1 mg/kg/day for ≤8 weeks

Facts to keep in mind

- Pulmonary Renal syndromes are diverse and can be FATAL.
- If bleeding is occurring from both the lungs and kidneys then these patients need to be in the ICU and get treatment FAST otherwise they will die.
- In difficult cases with vague symptoms, sometimes an early renal biopsy can make all the difference

على قدر الهدف يكون الانطلاق

ففي

" طلب الرزق قال:" فامشوا

" وللصلاة قال:" فاسعوا

" وللجنة قال:" وسارعوا

"وأما إليه فقال:"ففروا إلى الله

THANK YOU